METABOLISM AND DISEASE

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The preceding lectures of this series have been particularly instructive to one interested in metabolism primarily from the standpoint of disease. They have added to the principles which are employed in determining metabolic changes. Likewise they have cleared certain ill-understood manifestations of morbid processes. In this manner has advancing metabolic science enabled medicine better to comprehend the nature of disease. Awareness of this newer knowledge enables the surgeon, if he wishes, to escape an altogether too prevalent empiricism.

A number of diseases have been designated "idiopathic". This has resulted from a lack of understanding of the nature of the cause of the disturbance. As knowledge advances and as underlying principles are recognized, "*new*" diseases are gradually being separated from this group, isolated and defined as entities. It is obvious that such diseases are not "new". It is our discernment that is new, as an enlightened search of the older literature soon reveals. Metabolic investigation has been of especial service in this manner. Such a "new" disease is hyperparathyroidism.

HYPERPARATHYROIDISM.

Over fifty years ago a disabling, deforming disease of bone was recognized and reported (1). At first this was regarded as a peculiar form of osteomalacia, a wasting bone disease. Other instances were observed. In 1891 it was thoroughly described and given place as a disease entity by von Recklinghausen (2). It became further differentiated from other diseases presenting bone lesions. Owing to the presence of demonstrable areas of localized bone absorption, many of which contained loose fibrous tissue, it became known as osteitis fibrosa cystica. Since the bone cysts, rather than solitary, were widespread in their distribution, the modifying term "generalizata" was

added. Thus "von Recklinghausen's disease of bone" came to be recognized as involving the skeleton as a whole.

The earlier descriptions were of more advanced instances of this rare disease. These were, and are, the more readily recognized. In advanced cases the bones become demineralized. This is readily demonstrated by roentgenologic study. The local cysts may even contain areas of giant cells (3). There results an obvious weakening of the bones and an increased incidence of fractures.

In the early descriptions of the disease no mention is made of the existence of an associated parathyroid tumor. This is quite understandable, since the parathyroids were not discovered until 1880 (4). Hypoparathyroidism was only recognized in 1896 (5). The relationship to calcium metabolism was established even later (6).

Askanazy had doubtless seen an instance of the disease with an associated parathyroid adenoma (7). However, it was Erdheim's experimental studies that definitely related the parathyroids to bone disease (8). Erdheim, however, had regarded the parathyroid enlargement as a compensatory hyperplasia, and as subsequent to the bone disease, which he considered primary. Under the influence of Erdheim's hypothesis, Mandl (9) had made a homoplastic transplant of four normal parathyroids to a bed-ridden patient with von Recklinghausen's disease. The clinical symptoms, however, were definitely aggravated. Mandl then decided that the enlarged parathyroids might be the cause and not the effect of the disease. At a subsequent operation he discovered a parathyroid tumor, behind the thyroid gland. He removed it and also the transplanted parathyroids. This was followed by steady clinical improvement of the patient.

Following this striking clinical proof of the essential nature of von Recklinghausen's disease of bone, numerous similar instances were reported. About forty cases have now been studied and recorded (7, 12). Barr and Bulger (10), on the basis of clinical and experimental evidence, were the first to apply the term "hyperparathyroidism" to this rare disease.

The disease has now been reproduced experimentally (7) by administering, both acutely and chronically, Collip's (11) parathyroid extract known as "parathormone." It is even possible to produce, particularly in dogs, the characteristic bone cysts, as well as the evidence of generalized demineralization.

There are several diseases which are characterized clinically by the demineralization of bone. Compere (12a) has tabulated the principal features of seven of these. According to his studies, "hyperparathyroidism" presents five pathognomonic findings. These are: 1. A tumor of one or more parathyroids. 2. A negative calcium balance. 3. Increase in the urinary excretion of calcium. 4. Retention of sulphur. 5. The remaining parathyroids are normal grossly and microscopically. It may be added that the serum calcium is usually, although not always, elevated, and that the serum phosphorus is usually, although not always, lowered.

In this manner, too briefly sketched, has a "new" disease arisen from the "idiopathic" wasting diseases of bone. It is clearly a disorder in which there is a disturbance of calcium metabolism. The cause is a hyperfunctioning parathyroid.

IODINE METABOLISM AND THYROID DISEASE.

That a relation exists between the function of the thyroid gland and the metabolism of iodine is now undeniable. Within the past decade the nature of this relationship has been greatly clarified. Clarification has resulted, to a certain extent, from studies which have been made upon the effects of iodinization in the treatment of goiter (13). More has been learned, however, from the development of more accurate micromethods, permitting the determination of the minute amounts of iodine normally present within food, water, and air, as well as within the blood, urine and tissues (24).

The ancient use of burnt sponge in the treatment of goiter was a fortunate empiricism. Courtois discovered iodine in 1811, due to the fact that he used a lye made from seaweed, and the contained iodine corroded his copper vats. Soon after, Davy demonstrated the presence of iodine in sponges and other forms of marine life. As a natural consequence Coindet, a Swiss physician residing in Geneva, used iodine, in 1820, for the treatment of goiter (14). Since Coindet, iodine and the goiter problem have been inseparable.

Numerous subsequent investigations led to Prevost's theory in 1849. This indicated a relationship between iodine deficiency and thyroid overactivity resulting in goiter. The theory was substantiated by the work of Chatin (15). This led to the extensive use of iodized salt by the French in 1860, in an attempt to prevent the occurrence of goiter in the school children of

three departments of France (14). The ill results of this huge experiment led to abandonment of the practice. Advancing knowledge concerning the relationship between iodine and thyroid disease was consequently checked, and during the ensuing thirty-five years there arose other theories as to the nature of goiter. It was during this thirty-five year period (1860–1895) that the infection theory gained credence, doubtless due to the contemporary influence of Pasteur.

Impressed by the demonstrated interrelationship between the thyroid, goiter, and iodine, Theodore Kocher, eminent Bernese surgeon, assigned to one of his assistants the task of investigating the presence of iodine within the thyroid gland. The assistant failed. He found no iodine within the gland and thus missed making a discovery of fundamental significance. In 1895 Baumann, a biochemist, demonstrated the presence of quantities of iodine within the thyroid gland (16). As final scientific proof, Baumann actually isolated this iodine from the thyroid and demonstrated it, in its characteristic violet vapor form, in tubes (17). The significance of his contribution was quickly appreciated. Iodine in its relation to thyroid function recovered its lost prestige. The prophylactic use of iodine, properly controlled, in goiter, again became popularized. Marine and his associates (18) obtained excellent results in Ohio, as you are aware, by administering small doses of iodine. Other investigators in other countries were likewise successful (19). The lost ground was apparently recovered.

In 1919 Kendall isolated thyroxin (20). This crystalline substance, isolated from the thyroid gland, possessed certain of the physiologic properties of the dried whole gland. The isolation was repeated by Harington (21), who determined the correct molecular structure. Working from this structural formula, he succeeded in synthesizing thyroxin (22). Thyroxin, natural or synthetic, is 65 per cent iodine.

It seems obvious that the next forward step in determining more definitely the relationship between the thyroid and iodine should be an investigation of iodine metabolism. At once there arose the necessity of developing methods sufficiently sensitive, and at the same time sufficiently accurate, to determine the minute amount of iodine normally present within the ingesta, within the blood, within living tissues and within the excreta. This problem had been previously attempted by Chatin (15); however, his work had been doubted.

The iodine content of the thyroid gland itself was readily determined by the older, coarser methods, owing to the relatively high iodine concentration (23). This did not hold for the blood. Davy had originally separated and determined the iodine present in sponges by first ashing the organic material. The principle of his method, with various modifications, has since been widely followed. For decades, numerous methods had been devised for the determination of the iodine content of food, water, and air (24). None of these, however, was sufficiently delicate even to detect the minute amount of iodine normally present within the ordinary quantities of blood used for analyses.

During the first decade of this century advancing goiter research created an acute demand for an adequate micromethod. In 1922 the Swiss Goiter Commission, consequently, requested von Fellenberg, chemist of the Bureau of Hygiene, to develop such a method. He devised, perfected, and eventually synthesized the known existing quantitative procedures into an adequate micromethod for the determination of iodine (24). This will determine one ten-thousandth of a milligramme, 0.0001 mg. Two of von Fellenberg's pupils, Sturm (25) and Lunde (26), soon applied this method to a study of the blood, particularly in patients with thyroid disease. Thus was opened the way for a new approach to our conception of thyroid function in health and disease.

Following Baumann's discovery, numerous investigators had determined the iodine content of normal and of goitrous thyroid glands (27). Kendall and others (28) had observed a seasonal variation in the iodine content of the thyroid. This was lowest in the winter and spring and highest in the summer and autumn. These findings, by the way, correspond to what we now know of the associated blood iodine level (Sturm).

In investigating the intermediary metabolism of iodine, it was inevitable that attention should be directed to the blood. In 1899 Gley and Bourcet (29) unable to demonstrate iodine in 100 to 200 cc. samples, used a liter of dog's carotid blood for their analyses. They thus were able to demonstrate the presence of iodine in mammalian blood. They regarded it as a normal constituent of the blood stream. This was subsequently confirmed by some but denied by others (30). It was a matter of method. The earlier analyses were quantitatively inaccurate as judged by the results of modern micromethods.

The "*first modern figure*" for the blood iodine is that of Kendall, 13 gamma per cent for ox blood (31). The normal iodine content of blood is so minute that the term *gamma* is used to designate its unit. One gamma equals one one-thousandth of a milligramme, 0.001 mg. The normal iodine content of human blood in the Chicago district we have found to be about 12 gamma per cent, or .012 milligrammes in 100 cc. of blood (32). Attempts have been made at separating the iodine of the blood into an alcohol insoluble "organic" portion or one presumably in protein combination, and an "inorganic" portion or one which is alcohol soluble (33).

From an extensive investigation which our group has made during the past four years, it is apparent that a definite interrelationship exists between thyroid activity and the blood iodine niveau (34). In this our findings confirm those of Sturm and of Lunde. I wish to present, at this time, certain of the results which we have obtained in determining the blood iodine level of normal individuals and of over 150 patients with various diseases of the thyroid gland. These analyses have all been made by Dr. Chester Davis, Dr. Versa Cole, and Mr. Francis Phillips. Dr. Davis spent, at the commencement of our work, five months experimenting with and developing the method before it was applied to the blood of patients. The method he developed (35) was essentially that of von Fellenberg (24). Mr. Phillips has made important additions. It is possible to determine one ten-thousandth of a milligramme of iodine. Contrary to general opinion, the technical difficulties encountered concern mainly iodine loss rather than contamination.

Before considering the blood iodine data, several facts should first be recalled and emphasized. The diffusely enlarged, hyperplastic gland of untreated Grave's disease is ordinarily iodine-poor (27). It contains, as a rule, less iodine than the normal thyroid gland. Little or no colloid is present (36). This represents the overfunctioning thyroid. The amount of iodine within the gland increases from three to ten times following the customary preoperative administration of iodine (Lunde and Holst). This is accompanied by filling of the alveoli with colloid.

The normal blood iodine ranges from 8.5 to 16.2 gamma per cent, averaging 12 gamma per cent (37). This statement is based upon 34 determinations made upon twenty-eight

individuals with no evidence of thyroid dysfunction. Eight determinations made on six normal persons ranged between 8.9 and 13.8 gamma per cent, averaging 12 gamma per cent. It is necessary to determine the blood iodine of women in the intermenstrual period, since there is a rise in the blood iodine during the onset of menstruation (38). Thirteen determinations made on ten hospital patients on ordinary hospital diets revealed a range of from 8.5 to 13.4 gamma per cent and an

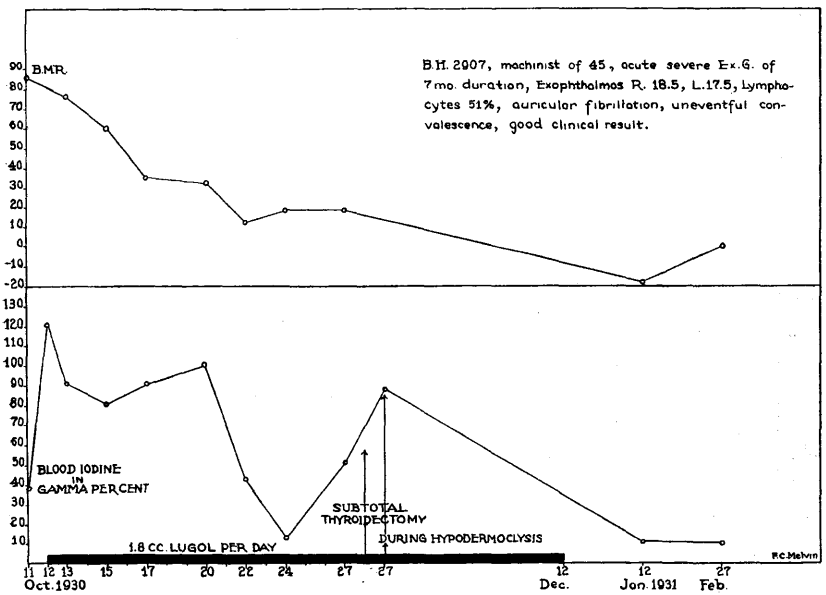

FIGURE 1.

THE BLOOD IODINE IN EXOPHTHALMIC GOITER.

The blood iodine is elevated previous to medication (normal = 12 gamma per cent). It rises upon lugolization. It is high during iodine administration by hypodermoclysis. It falls to a low normal level subsequent to subtotal thyroidectomy and the cessation of lugolization. The elevated B. M. R. falls upon lugolization. It remains low after an adequate thyroidectomy.

average of 12.3 gamma per cent. Iodized salt was not used in the hospital diet. No significant change was noted in the blood iodine of patients with cancer. Thirteen determinations made on twelve patients in the Out-Patient Department gave a range of from 8.5 to 16.2 gamma per cent, averaging 11.4 gamma per cent.

In acute hyperthyroidism, known clinically as Grave's disease, there is a marked elevation (Figure 1) of the blood

iodine (39). Sixteen determinations made on eleven of these unmedicated patients revealed a range of from 16.9 to 40.1 gamma per cent, or an average of 27.1 gamma per cent. The average basal metabolic rate in these eleven patients was plus 50. No direct correlation was observed between the height of the basal metabolic rate and the blood iodine level. We have thus far made no attempt to fractionate this high blood iodine into "organic" and "inorganic" portions.

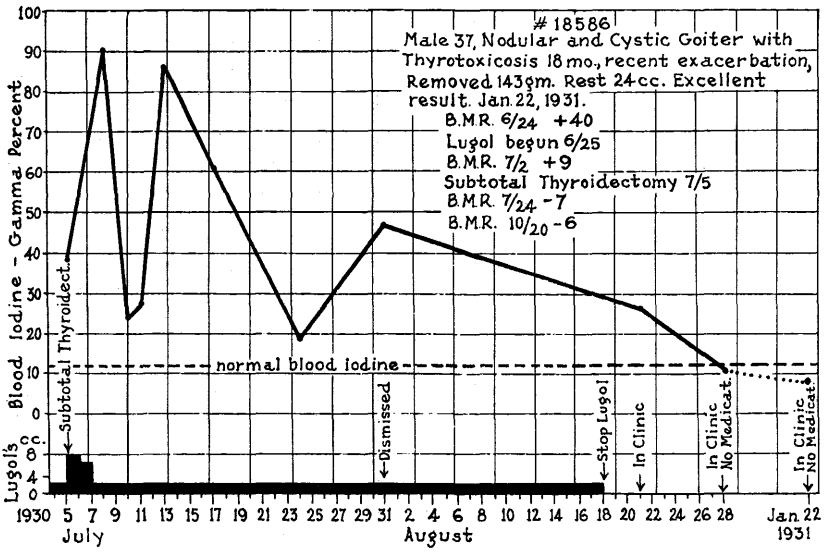

FIGURE 2.

THE BLOOD IODINE IN TOXIC NODULAR GOITER.

Following subtotal thyroidectomy the blood iodine remains elevated so long as lugolization is continued. It falls to a low normal level after adequate thyroidectomy and cessation of iodine medication.

After an adequate thyroidectomy, with subsequent relief of the symptoms of the hyperthyroidism, the elevated blood iodine falls to a low normal range (Figure 1). Fifteen determinations made on twelve operated patients revealed a range of from 8.7 to 14.3 gamma per cent, or an average of 10.4 gamma per cent. The basal metabolic rate in these patients averaged minus 6.

In the more chronic and less severe form of hyperthyroidism occurring in patients with nodular goiters, the blood iodine is also elevated, (Figure 3). Eleven determinations on eleven of these patients revealed a range of from 13.1 to 38.1 gamma per cent, averaging 22 gamma per cent. The average basal

metabolic rate was plus 26. Thus chronic hyperthyroidism is accompanied by a lesser elevation of the blood iodine, as well as by a lesser elevation of the basal metabolic rate. Likewise,

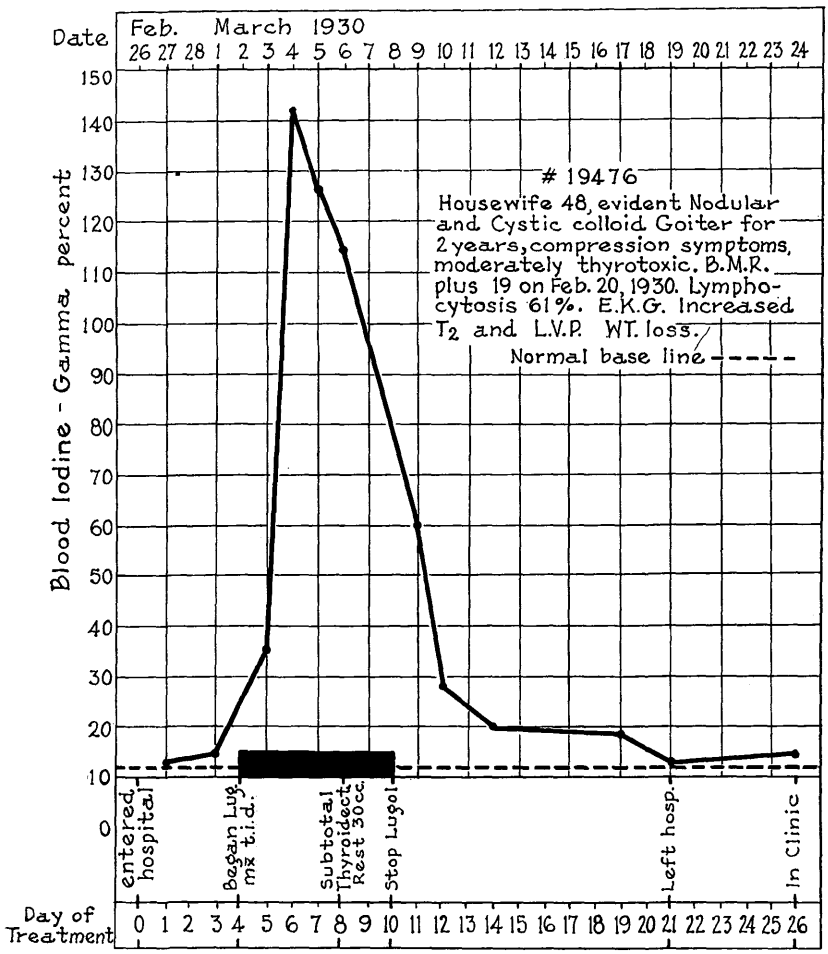

FIGURE 3.

THE BLOOD IODINE IN MODERATELY TOXIC NODULAR GOITER.

The premedication level is above normal. A marked rise occurs upon lugolization and continues so long as iodine is administered. There is still some elevation two weeks after thyroidectomy and the cessation of lugolization.

in toxic nodular goiter, no direct correlation was observed between the blood iodine and the elevated basal metabolic rate. After these patients have submitted to an adequate

thyroidectomy, with the subsequent symptomatic relief, the blood iodine falls to a low normal level, (Figure 2). Twenty-three determinations, made on twelve of these patients, revealed a range of from 5.5 to 16.9 gamma per cent, averaging 10.4 gamma per cent. The average basal metabolic rate in these twelve patients was minus 4. It is thus apparent, that when hyperthyroidism is controlled by adequate removal of the over-functioning gland, the elevated blood iodine falls to a low normal level. This is shown in Figures 1 and 2.

If the thyroidectomy is inadequate, the blood iodine does not fall to a low level. It also remains elevated between the stages of a two stage lobectomy. In four determinations made on four of these patients, the range was from 19.4 to 32 gamma per cent, averaging 26.1 gamma per cent. The average basal metabolic rate in these patients was plus 31.

Nontoxic nodular goiter, presenting no symptoms of hyperthyroidism, is accompanied by a low normal range of the blood iodine. In eighteen determinations made on ten of these patients, the range was from 6.3 to 12.7 gamma per cent, averaging 10.4 gamma per cent. The average basal metabolic rate in these ten patients was minus 4. Following partial thyroidectomy for nontoxic, nodular goiter, little eventual change occurs in the elevation of the blood iodine. This is shown in Figure 3. In these patients more of the thyroid is left behind than in those patients with toxic goiter.

The blood iodine is variable in its elevation in various other diseases. It is definitely elevated in lymphatic leukemia. It is to be remembered that in this disease there is an elevation of the basal metabolic rate, of the lymphocyte count of the blood, and that beneficial effect ensues after iodine treatment. We may now add that the blood iodine is elevated (40). This striking parallelism between hyperthyroidism and lymphatic leukemia is worthy of further investigation.

In those patients who, normal metabolically, develop exophthalmos subsequent to an adequate thyroidectomy, the blood iodine is normal (40). In unmedicated hypothyroidism the blood iodine is low (40). In eleven determinations made on eight of these patients, the range was from 7.2 to 11 gamma per cent, averaging 9.4 gamma per cent. The average basal metabolic rate was minus 16. When these patients are given desiccated thyroid by mouth, there occurs, along with the clinical improvement, a rise in the iodine content of the blood.

It is difficult to dissociate this rise from the amount of iodine administered in the desiccated thyroid. Immediately following administration, there ensues a sharp rise in the blood iodine. This precedes that of the basal metabolism. In patients with treated hypothyroidism the blood iodine is elevated. This elevation is greater at first and becomes stabilized at a high normal level after continued desiccated thyroid administration.

Members of the same family, with varying states of thyroid function due to disease, present striking variations of the blood iodine. In one family investigated, the blood iodine of the mother was high. She had toxic nodular goiter. The blood iodine was normal in one son with no evidence of thyroid disease and low in another son and daughter who had diffuse goiters with hypothyroidism.

Immediately following a thyroidectomy, there ensues a fall in the blood iodine. It remains to be seen whether this is directly the result of the removal of an excess amount of the secreting thyroid tissue.

In children with acute hyperthyroidism, the blood iodine is definitely elevated (41). It responds to iodine medication and thyroidectomy as does the blood iodine in adults. Subsequent to thyroidectomy for toxic goiter, the blood iodine remains high so long as iodine medication is continued. Upon cessation of iodine medication, however, it falls to a low normal level, provided an adequate thyroidectomy has been made. This effect is presented in Figure 1.

Judging from an extensive clinical study of the blood iodine in patients with varying states of thyroid activity, there is a definite relationship between the level of the blood iodine and thyroid function (40).

DEMINERALIZATION.

The significance of other blood electrolytes in relation to disease is also deserving of our attention. Changes in the normal concentration of certain ions, or fluctuations in the balance between others, are associated with certain morbid processes occurring spontaneously or produced experimentally. Subsequent to surgical operations, during which ether is used as the anesthetic, there ensue extensive changes in the calcium-potassium ratio of the blood (42). These are accompanied by a period of post-operative lethargy, and a marked tissue thirst. Calcium loss, sufficient to result in osteoporosis, may ensue

following the continuous loss of bile subsequent to the establishment of a chronic biliary fistula (43). The blood bromine is now receiving clinical attention (55).

The chloride of the blood, since it is the most prevalent ion and the more readily determined by various analytical methods, has been particularly studied. An extensive literature has already accumulated. The hypochloremia subsequent to upper intestinal obstruction has been frequently confirmed (44). A similar lowering of the blood chloride is associated with the fatal effect of the total loss of gastric juice (45). Orr and Haden (46) report that the blood chloride is also lowered in dogs with fatal experimental peritonitis. We have observed a low blood chloride accompanying a strangulated hernia of the omentum, and in cases of acute diffuse peritonitis. The blood chloride is low despite the blood concentration of the so-called toxemia following extensive superficial burns (47). The fluid within the blisters has a chloride concentration higher than that of the blood plasma. The symptoms of heat cramps, called also miner's cramp, stoker's cramp, or fireman's cramp, are initiated by a marked loss of perspired chloride and are prevented by drinking saline or relieved by the administration of salt solutions (48). The symptoms of "water intoxication" as studied and described by Rowntree (49) are relieved by saline intravenously. In pneumonia the serum chloride is lowered and the urinary excretion of chloride decreases or even fails. In view of these and of other similar clinical findings, it appears that the disturbance in chloride metabolism associated with these morbid states is possibly of more than subordinate importance.

Various crystalloids may be readily dialyzed away from the circulating blood through celloidin tubes inserted in the course of the blood stream. This process, called *vividiffusion*, was devised by Abel, Rowntree, and Turner (51). Dialysis also readily occurs through the peritoneum. Cohnheim (52) found that chloride soon appears in glucose solutions injected intraperitoneally in rabbits. This is likewise true when varying concentrations of cane sugar are employed (53). When distilled water is injected intraperitoneally, a higher per cent of chloride, up to 0.63 per cent, is deviated from the blood stream and the blood chloride falls (54). The intraperitoneal water soon becomes isosmotic and obtains up to 1.5 per cent of albuminous substance as well as numerous cells. Achloride electrolytes, as

well as organic crystalloids, are likewise dialyzed from the blood stream (54). Consequently, it has been possible, experimentally, to demineralize rabbits by perfusing distilled water through the peritoneal cavity (50, 60).

The transperitoneal perfusion of distilled water at body temperature at the rate of 500 cc. per hour results, within an hour, in an increase in the respiratory rate and the appearance of localized fibrillary twitchings of the muscles (50). These become more generalized, and are followed by clonic and tonic convulsions of increasing severity. Spasmodic contractions of the diaphragm occur, and the animals ordinarily die after from two to five hours of perfusion. The blood chloride falls. The carbon dioxide combining power of the plasma falls. There is a moderate rise in the N. P. N., and a slight elevation of the urea. The secretion of urine soon diminishes and finally completely ceases. The development of the symptoms and of the lethal effect are not due to hypoglycemia since addition of 0.12 per cent glucose to the perfusion water in other experiments was without preventive effect.

Transperitoneal perfusion of Ringer's solution, or of isosmotic pure sodium chloride, with or without glucose, resulted in the development of no muscular twitchings or convulsions. These animals were alive and in good condition when the experiments were terminated at the end of eight to ten hours. The blood chloride was slightly elevated. There was a continuous secretion of urine, or even a moderate diuresis. In one of the sodium chloride perfusion experiments the serum calcium fell to 2.9 mg. per 100 cc. of blood without evidence of tetany.

The transperitoneal perfusion of 4.2 per cent glucose resulted in increased respirations, muscular twitchings and tremors, convulsions and eventually death in from two and one-half to seven hours. The terminal blood chloride was low. There was an enormous rise in the blood sugar. Perfusion of 0.45 per cent sodium chloride and 2.1 per cent glucose had no such lethal effect and the animals lived.

The perfusion of Ringer's solution with glucose, but *without sodium chloride*, resulted in increased respirations, muscular twitchings and convulsions and eventual death. The blood chloride fell. The secretion of the urine diminished and then ceased.

An adequate amount of sodium chloride was eventually supplied to the blood stream during the transperitoneal per-

fusion with distilled water. This was accomplished by the timed intravenous injection of 2.5 per cent pure sodium chloride by means of the Woodyatt pump. It was found best to inject a 2.5 per cent solution of pure sodium chloride at the rate of 1 cc. per minute into one of the cannulated jugular veins. When too concentrated solutions were used, e. g., 9.0 per cent, thrombosis occurred locally and was even followed by pulmonary embolism. If the solution is too dilute, sodium chloride is not supplied as rapidly as it is dialyzed away; also, too much water must be simultaneously injected. The continuance of renal secretion is apparently an important factor in the success of these experiments.

By this method it was possible to keep the animals alive. One animal lived seventeen and one-half hours, more than five times as long as during the transperitoneal perfusion of distilled water alone. Occasional mild muscular fibrillation was noted, but no severe tremors or no convulsions. A marked diuresis was observed. There was a slight fall in the whole blood chloride. There was no tetany although the serum calcium fell to 3.8 mg. per 100 cc.

In succeeding experiments the combined intravenous infusion and transperitoneal perfusion were similarly maintained for twelve hours without the development of notable symptoms. At the end of that time the intravenous injection of pure sodium chloride was stopped, but the transperitoneal perfusion of distilled water with glucose continued. Muscular twitchings then developed, became more severe and finally convulsions occurred and death followed after five hours of transperitoneal perfusion alone.

It is difficult to make any greatly inclusive judgments as to the bearing of these experiments upon our daily clinical problems. So much is unknown, particularly regarding the associated physico-chemical blood changes. Consequently, it is with some hesitation that I shall consider their significance in four conditions which we encounter in the post-operative management of our surgical cases: dehydration, anuria, tetany, and hypochloremia.

Dehydration is frequently evoked to explain the results of the extensive loss of fluid by profuse sweating, in extensive burns, by vomiting, diarrhea, or through the various gastro-intestinal fistulae. On the other hand, we must be careful to remember that all these fluids have a considerable mineral

content which likewise is simultaneously lost to the organism. In replacing this fluid loss, we do not administer distilled water, but rather salt solutions.

During the past few years, we have analyzed chemically the body fluids found in various morbid conditions such as ascites, hydrothorax, pericardial effusion, hydrocele, blisters following burns, synovial effusions, effusions in bursae, ovarian cysts and tendon sheaths (56). Nearly all of these have a high mineral content. The copious intestinal fluid found in the paralytic ileus accompanying peritonitis has a high mineral content, likewise the intestinal fluid above a mechanical obstruction or that draining from a jejunostomy. The loss of these fluids is thus accompanied by a considerable loss of minerals. As a consequence together with the dehydration, demineralization is to be considered. These experiments demonstrate certain of the effects of demineralization as produced by peritoneal dialysis. Consequently, in our replacement therapy, we should be aware of the demineralization associated with the loss of body fluids.

The treatment of the recurrent ascites of portal cirrhosis by biweekly paracentesis of the abdomen is of interest in this connection. So much as ten liters of fluid may be obtained at each tapping. It is not generally recognized that this fluid has a high mineral content. We have determined this as about 0.7 per cent (56). Thus every two weeks over 70 grammes of minerals are removed from the patient, as well as protein and other crystalloids.

The anuria associated with intestinal obstruction is commonly thought to be due to a "toxemia" which in some manner depresses the function of the kidney. Our experiments show, when the organism is being demineralized by the transperitoneal perfusion of distilled water, that the secretion of urine soon decreases and finally ceases. That this is not due to some toxic action upon the kidney is shown by the fact that the kidney resumes function upon the simultaneous administration of timed adequate salt solution intravenously (57). In a study of the mechanism of diuresis we found it possible to inhibit or even block the normal action of a theophyllin diuretic administered intramuscularly, by simultaneously injecting distilled water intraperitoneally (58). This intraperitoneal distilled water caused a rapid dialysis of salts from the blood stream and tissues into the artificial transudate. The minerals were thus

deviated. When the artificial transudate became isosmotic, a diuresis ensued. Diuresis is dependent to a great extent upon the state of the tissues (58). Changes in this state due to mineral loss may readily affect the function of the kidney. In this manner we would regard certain cases of postoperative anuria as due to a depletion of blood or tissue electrolytes rather than as resulting from some "toxic" or "reflex" (59) effect.

Various forms of tetany have been recognized clinically. Most commonly it is regarded as being associated with hypoparathyroidism and a lowered blood calcium. There has been a tendency to explain the various types of tetany upon this basis. We have produced tetany in animals by perfusing distilled water through the peritoneal cavity (50). This tetany may be relieved by the simultaneous intravenous injection of adequate pure sodium chloride. When pure physiologic saline is perfused through the peritoneal cavity, tetany does not usually occur even though the blood calcium falls (50). It would seem from our experiments and from a study of certain morbid states, that certain forms of tetany are associated with demineralization and particularly with an extensive loss of chloride.

The frequent occurrence of lowered blood chloride in various morbid conditions and the relief of the symptomatology in certain of these conditions by the administration of sodium chloride by mouth, by hypodermoclysis, or intravenously, indicate the significance of hypochloremia. It is difficult properly to evaluate with the evidence at hand the complex physico-chemical changes which occur in the blood and tissues of the animals which we have perfused with distilled water or various other solutions. The evidence, however, which we have, both from the literature and from these briefly presented experiments leads us to reemphasize the significance of the minerals to life and a state of well being.

The evidence for the significance of calcium and its relation to parathyroid function is convincing. Likewise the interrelation between thyroid function and iodine is inescapable. The specificity of chloride is not so clear.

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